

REMARKS

I. Status of the claims and support for the amendments

Claims 36 and 40 are currently amended.

Claims 53–55 are new.

Claims 36–55 are currently pending.

Support for the amendment of the specification is found in claims 45, 49, 51, and 52.

Support for the amendment of claims 36 and 40 is found at pages 6 and 9 of the specification and support for new claims 53–55 is found at pages 9 and 17 of the Specification and in the claims as originally filed.

II. Rejection under 35 U.S.C. §112

A. Claims 40–42 are rejected under 35 U.S.C. §112, first paragraph as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Specifically, the Examiner alleges that “[t]he specification does not provide support for use of polysaccharides having polymer charge density [sic] of <30%. Charge density range is addressed [on] page 9, and in Table 1 in regard to polyacrylamides rather than to polysaccharides.” Applicant responds as follows.

As currently amended, claims 40–42 no longer recite that the anionic polymer has a charge density of <30%. Accordingly, Applicant believes that this rejection has been overcome and may properly be withdrawn.

B. Claim 43 is rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to convey to one of skill in the art that the inventor, at the time the application was filed, had possession of the

claimed invention. Specifically, it is alleged that, "[t]he specification does not provide support for the concentration range of 20–30 ppm as claimed." Applicant respectfully traverses.

As a preliminary matter, Applicant believes that there is a typographical error wherein the rejection refers to claim "43" as containing the "20–30 ppm" limitation. According to Applicant's records, claim 43 contains no such limitation. Consequently, Applicant assumes that the rejection was meant for claim "45," which does contain the "20–30 ppm" limitation. Applicant's response is based on this presumption. If Applicant's presumption is in error, clarification is respectfully requested.

As modified by the above amendment, the Specification specifically recites that the anionic polymer may be present at a concentration of from "20–30 ppm". Moreover, support for this amendment to the Specification is found in claim 43, as originally filed. As set out in MPEP 608.01(I), Applicant is entitled to rely on the content of the original claims for what they disclose. Given, that the original claim 45 clearly disclosed that one embodiment of the invention comprised a composition having an anionic polymer concentration of from 20–30 ppm, Applicant believes that the Amendment to the Specification overcomes the rejection of claim 45, under 35 U.S.C. §112, first paragraph. Consequently, Applicant respectfully requests that this rejection be withdrawn.

C. Claims 49, 51, and 52 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter not described in the specification. The rejection specifically alleges that "[t]he specification does not provide support for the combination of specific ranges of parameters as described. Applicant respectfully traverses.

In view of the above amendment to the Specification, Applicant contends that the Specification now contains the required written description. Furthermore, as similar to

Applicant's arguments in part II.B., *supra*, the material incorporated into the Specification by the Amendment finds support in claims 49, 51, and 52, as originally filed. Accordingly, Applicant believes that this rejection of claims 49, 51, and 52 has been overcome and may now properly be withdrawn.

D. Claims 36 and 40-50 are rejected under 35 U.S.C. §112, first paragraph as allegedly not being enabled by the specification. Specifically, the rejection alleges that:

the specification, while being enabling for polyacrylamide and potato starch, does not reasonably provide enablement for other polymers, in particular, other polysaccharides. The working examples and guidance in the specification focused on use of polyacrylamide; also use of potato starch is addressed in example 6. In regard to polysaccharides neither polysaccharides other than potato starch are described, nor their charge density and selection are addressed. The specification does not enable use of any other anionic polymers and the artisan is not enabled to use the invention commensurate in scope with these claims.

Applicant respectfully traverses.

As set out in MPEP Chapter 2100:

Any analysis of whether a particular claim is supported in an application requires a determination of whether that disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention. The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation, v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)

MPEP 2164.01. Applicant contends the Specification provides sufficient disclosure to enable the claims as currently amended. The Specification sets out all of the criteria necessary to enable one of ordinary skill in the art to make and use the invention. For example, the Specification clearly describes the critical importance of using an *anionic* polymer as the flocculant. Moreover, this description is supported by Example 4 and Table 4 which demonstrate the effect of polymer charge density on the performance of the flocculant when used according to the

instant invention. In view of this example, Applicant asserts that the Specification contains all the description necessary to enable one of ordinary skill in the art to make and use the invention "without undue experimentation." "The test of enablement is not whether any experimentation is necessary, but whether if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976)." *Id.* (emphasis added). In view of this standard, it is Applicant's position that this satisfies the *Wands* test for enablement are satisfied. That is the claims are enabled because the Applicant has set out in the specification all of the factors to be considered in determining whether an anionic polymer is suitable for use in according to the instant invention.

One skilled in the art seeking to carry out the invention commensurate with the claims would simply have to determine whether a flocculant was likely suitable by determining whether it met the required parameters of polymer charge density and average molecular weight, as set out in the Specification. The skilled artisan could then determine whether the flocculant was suitable for the desired purposes, by routine experimentation. As noted in MPEP 2164.01, "[t]he fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd sub nom.*, *Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985).

Furthermore, the MPEP 2164.01(b) states that

as long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. §112 is satisfied. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Failure to disclose other methods by which the claimed invention may be made does not render a claim invalid under 35 U.S.C. §112. *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524, 1533, 3 USPQ2d 1737, 1743 (Fed. Cir.), *cert. denied*, 484 U.S. 954 (1987).

In sum, Applicant has discovered the surprising fact that somatotropin compositions comprising anionic flocculants of a particular charge density are very effective at removing unwanted impurities from the desired somatotropin monomers. Furthermore, Applicant has demonstrated provided examples of such compositions using multiple flocculants (*e.g.*, see Table 4). It is well within the ability of the ordinarily skilled artisan, using routine experimentation, to employ the criteria set out by Applicant's to flocculants not explicitly described in the Specification. Accordingly, the use of such flocculants is enabled, by the instant Application (in fact, it is only through the instant Specification that the skilled artisan knows of the beneficial use of these flocculants). Accordingly, the instantly pending claims are believed to be fully enabled.

In view of the foregoing, Applicant contends that the rejection of claims 36 and 40-50 has been overcome and may now properly be withdrawn.

III. Rejections under 35 U.S.C. §103

A. Claims 36, 40-48, and 50 are rejected under 35 U.S.C. §103(a) as allegedly being obvious in view of Oechslein *et al.* (*Internt'l Journal of Pharmaceutics* 139:25-32, 1996). The rejection states that Oechslein *et al.* teaches "formulations comprising *somatostatin* analog *ostreotide* [sic] and absorption modifier, such as starch. See abstract. As such the components of the referenced composition read on instantly claimed composition comprising somatostatin and anionic polymer, such as starch" (emphasis added). Applicant respectfully traverses.

MPEP 706.02(j) provides the following criteria which must be met in order to establish obviousness.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must

be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991) (emphasis added).

In response to the rejection, Applicant first points out that the instantly pending claims are drawn to somatotropin (or growth hormone) not to somatostatin. Furthermore, the somatostatin octreotide described in Oechslein *et al.* is a cyclic octapeptide, that is eight amino acids (*see* description of Novartis' Sandostatin® brand octreotide provided herewith) whereas somatotropins typically comprise 191 amino acid residues.

Applicant asserts that there is nothing in the disclosure of Oechslein *et al.* which would motivate one of ordinary skill in the art to modify the composition therein to comprise the ST monomers and oligomers of the instantly pending claims. Accordingly, the cited reference fails to meet the criteria set out in MPEP §706.02(j). Therefore, Applicant contends that the rejection of the claims as being obvious in view of Oechslein *et al.* has been overcome and may now properly be withdrawn.

B. Claims 36, 40, 41, 43–48, and 50 are rejected under 35 U.S.C. §103(a) as allegedly being obvious over Takama *et al.* (US 5,929,027). The rejection states that “Takama *et al.* teaches sublingual tablets comprising physiologically active peptides, such as, e.g., somatostatin (see col. 3, line 19), and excipients, such as starches or modified celluloses (carboxymethylcellulose, hydroxypropyl cellulose, etc – see col. 4, lines 22-23).” Applicant respectfully traverses.

Applicant points that nowhere does Takama *et al.* describe a composition comprising somatotropin, much less a composition comprising soluble somatotropin monomers, precipitated somatotropin oligomers, and an anionic polymer. Accordingly, Applicant contends that Takama

et al. provides no motivation to one of skill in the art to provide a composition as instantly claimed.

The instantly claimed compositions were formulated to provide an efficient and effective way to separate active soluble somatotropin monomers from inactive, precipitated ST oligomers and other bacterial cell debris. There is nothing in the Takama *et al.* which teaches or suggests compositions such as those currently claimed. Further, Takama *et al.* does not teach all of the claimed limitations as required by MPEP 706.02(j). Accordingly, Applicant asserts that Takama *et al.* does not render the rejected claims obvious under 35 U.S.C. §103(a). Therefore, Applicant respectfully submits that this rejection has been overcome and requests that it be withdrawn.

C. Claims 36–39, 43–48, and 50 are rejected under 35 U.S.C. §103(a) as allegedly being obvious over Churchill *et al.* (US 4,942,035). Specifically, the rejection states that Churchill *et al.* “teaches aqueous suspensions of physiologically active peptides, such as, e.g., somatostatin (see col. 3, line 1, emphasis added), and hydrophilic polymer B, such as polyacrylamide (see col. 4, line 25), the latter might be copolymerized with another hydrophobic polymer (see col. 3, lines 25–31). The polymer used in the composition is of molecular weight of >5000. Applicant respectfully traverses.

As currently amended, the pending claims are drawn to compositions comprising soluble ST monomers, precipitated ST oligomers, and an anionic polymer. There is nothing in Churchill *et al.* which teaches or provides any motivation to produce compositions comprising these constituents. Moreover, Churchill *et al.* does not teach or suggest all of the limitations of the currently claimed invention. Therefore, Applicant asserts that Churchill *et al.* cannot properly be viewed as rendering claims 36, 40–45, and 50 obvious. That is, Churchill *et al.* fails to meet at least two of the criteria set out in MPEP706.02(j) as being required to establish a *prima facie*

case of obviousness. For this reason, Applicant submits that the rejection of these claims as being obvious over Churchill *et al.* has been overcome and may properly be withdrawn.

D. Claims 36, 40–45, and 50 are rejected as allegedly being obvious over Holmberg *et al.* (WO 98/28336). Specifically, the rejection states that “[t]he reference teaches compositions comprising conjugates of somatostatins and charged polysaccharides. As the composition instantly claimed is described using open language ‘comprising’ without specifying whether the components are present separately or connected, the referenced composition is considered as reading on the claimed composition.” Applicant respectfully traverses.

As noted in the abstract of Holmberg *et al.*, the reference is drawn to “polysaccharide-somatostatin-analogs and derivatives thereof.” The disclosure of the cited reference is not related to somatotropin (growth hormone). Accordingly, there is nothing in the reference which teaches or suggests a composition comprising soluble somatotropin monomer, precipitated somatotropin oligomers, and an anionic polymer (especially a composition where the anionic polymer and precipitated oligomers are aggregated). Accordingly, Holmberg *et al.* fails to meet the criteria required to establish a *prima facie* case of obviousness. Specifically, Holmberg *et al.* provide no teaching or motivation to provide the claimed compositions and it does not teach all of the limitations of the currently claimed compositions.

For the foregoing reasons, Applicant believes that the rejection of the claims under 35 U.S.C. §103(a) as being obvious over Holmberg *et al.* has been overcome and may now properly be withdrawn.


IV. Conclusion

In view of the foregoing amendments to the specification and claims and in further view of the arguments set out above, Applicant believes that all rejections of the claims have been

overcome and should be withdrawn. Accordingly, Applicant respectfully request a favorable reconsideration of the instant application and the issuance of a "Notice of Allowance" therefor.

The Examiner is invited to contact the undersigned patent agent at (713) 787-1589 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,



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Date: October 3, 2003



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Sandostatin[®]
octreotide acetate

Injection

Rx Only

DESCRIPTION

Sandostatin[®] (octreotide acetate) Injection, a cyclic octapeptide prepared as a clear sterile solution of octreotide, acetate salt, in a buffered lactic acid solution for administration by deep subcutaneous (intrafat) or intravenous injection. Octreotide acetate, known chemically as L-Cysteinamide, D-phenylalanyl-L-cysteinyl-L-phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-N-[2-hydroxy-1-(hydroxymethyl)propyl]-, cyclic (2→7)-disulfide; [R-(R*, R*)] acetate salt, is a long-acting octapeptide with pharmacologic actions mimicking those of the natural hormone somatostatin.

Sandostatin[®] (octreotide acetate) Injection is available as: sterile 1 mL ampuls in 3 strengths, containing 50, 100, or 500 mcg octreotide (as acetate), and sterile 5 mL multi-dose vials in 2 strengths, containing 200 and 1000 mcg/mL of octreotide (as acetate).

Each ampul also contains:

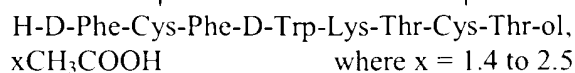
lactic acid, USP	3.4 mg
mannitol, USP	45 mg
sodium bicarbonate, USP	qs to pH 4.2 ± 0.3
water for injection, USP	qs to 1 mL

Each mL of the multi-dose vials also contains:

lactic acid, USP	3.4 mg
mannitol, USP	45 mg
phenol, USP	5.0 mg
sodium bicarbonate, USP	qs to pH 4.2 ± 0.3
water for injection, USP	qs to 1 mL

Lactic acid and sodium bicarbonate are added to provide a buffered solution, pH to 4.2 ± 0.3.

The molecular weight of octreotide acetate is 1019.3 (free peptide, C₄₉H₆₆N₁₀O₁₀S₂) and its amino acid sequence is:



CLINICAL PHARMACOLOGY

Sandostatin[®] (octreotide acetate) exerts pharmacologic actions similar to the natural hormone, somatostatin. It is an even more potent inhibitor of growth hormone, glucagon, and insulin than somatostatin. Like somatostatin, it also suppresses LH response to GnRH, decreases splanchnic blood flow, and inhibits release of serotonin, gastrin, vasoactive intestinal peptide, secretin, motilin, and pancreatic polypeptide.

By virtue of these pharmacological actions, Sandostatin[®] (octreotide acetate) has been used to treat the symptoms associated with metastatic carcinoid tumors (flushing and diarrhea), and Vasoactive Intestinal Peptide (VIP) secreting adenomas (watery diarrhea).

Sandostatin[®] (octreotide acetate) substantially reduces growth hormone and/or IGF-I (somatomedin C) levels in patients with acromegaly.

Single doses of Sandostatin[®] (octreotide acetate) have been shown to inhibit gallbladder contractility and to decrease bile secretion in normal volunteers. In controlled clinical trials the incidence of gallstone or biliary sludge formation was markedly increased (*see WARNINGS*).

Sandostatin[®] (octreotide acetate) suppresses secretion of thyroid stimulating hormone (TSH).

Pharmacokinetics

After subcutaneous injection, octreotide is absorbed rapidly and completely from the injection site. Peak concentrations of 5.2 ng/mL (100 mcg dose) were reached 0.4 hours after dosing. Using a specific radioimmunoassay, intravenous and subcutaneous doses were found to be bioequivalent. Peak concentrations and area under the curve values were dose proportional after intravenous single doses up to 200 mcg and subcutaneous single doses up to 500 mcg and after subcutaneous multiple doses up to 500 mcg t.i.d. (1500 mcg/day).

In healthy volunteers the distribution of octreotide from plasma was rapid ($t_{\alpha 1/2} = 0.2$ h), the volume of distribution (V_{dss}) was estimated to be 13.6 L, and the total body clearance ranged from 7 L/hr to 10 L/hr. In blood, the distribution into the erythrocytes was found to be negligible and about 65% was bound in the plasma in a concentration-independent manner. Binding was mainly to lipoprotein and, to a lesser extent, to albumin.

The elimination of octreotide from plasma had an apparent half-life of 1.7 to 1.9 hours compared with 1-3 minutes with the natural hormone. The duration of action of Sandostatin[®] (octreotide acetate) is variable but extends up to 12 hours depending upon the type of tumor. About 32% of the dose is excreted unchanged into the urine. In an elderly population, dose adjustments may be necessary due to a significant increase in the half-life (46%) and a significant decrease in the clearance (26%) of the drug.

In patients with acromegaly, the pharmacokinetics differ somewhat from those in healthy volunteers. A mean peak concentration of 2.8 ng/mL (100 mcg dose) was reached in 0.7 hours after subcutaneous dosing. The volume of distribution (V_{dss}) was estimated to be

21.6 \pm 8.5 L and the total body clearance was increased to 18 L/h. The mean percent of the drug bound was 41.2%. The disposition and elimination half-lives were similar to normals.

In patients with renal impairment the elimination of octreotide from plasma was prolonged and total body clearance reduced. In mild renal impairment (Cl_{CR} 40-60 mL/min) octreotide $t_{1/2}$ was 2.4 hours and total body clearance was 8.8 L/hr, in moderate impairment (Cl_{CR} 10-39 mL/min) $t_{1/2}$ was 3.0 hours and total body clearance 7.3 L/hr, and in severely renally impaired patients not requiring dialysis (Cl_{CR} <10 mL/min) $t_{1/2}$ was 3.1 hours and total body clearance was 7.6 L/hr. In patients with severe renal failure requiring dialysis, total body clearance was reduced to about half that found in healthy subjects (from approximately 10 L/hr to 4.5 L/hr).

Patients with liver cirrhosis showed prolonged elimination of drug, with octreotide $t_{1/2}$ increasing to 3.7 hr and total body clearance decreasing to 5.9 L/hr, whereas patients with fatty liver disease showed $t_{1/2}$ increased to 3.4 hr and total body clearance of 8.2 L/hr.

INDICATIONS AND USAGE

Acromegaly

Sandostatin[®] (octreotide acetate) is indicated to reduce blood levels of growth hormone and IGF-I (somatomedin C) in acromegaly patients who have had inadequate response to or cannot be treated with surgical resection, pituitary irradiation, and bromocriptine mesylate at maximally tolerated doses. The goal is to achieve normalization of growth hormone and IGF-I (somatomedin C) levels (*see DOSAGE AND ADMINISTRATION*). In patients with acromegaly, Sandostatin[®] (octreotide acetate) reduces growth hormone to within normal ranges in 50% of patients and reduces IGF-I (somatomedin C) to within normal ranges in 50%-60% of patients. Since the effects of pituitary irradiation may not become maximal for several years, adjunctive therapy with Sandostatin[®] (octreotide acetate) to reduce blood levels of growth hormone and IGF-I (somatomedin C) offers potential benefit before the effects of irradiation are manifested.

Improvement in clinical signs and symptoms or reduction in tumor size or rate of growth were not shown in clinical trials performed with Sandostatin[®] (octreotide acetate); these trials were not optimally designed to detect such effects.

Carcinoid Tumors

Sandostatin[®] (octreotide acetate) is indicated for the symptomatic treatment of patients with metastatic carcinoid tumors where it suppresses or inhibits the severe diarrhea and flushing episodes associated with the disease.

Sandostatin[®] (octreotide acetate) studies were not designed to show an effect on the size, rate of growth or development of metastases.

Vasoactive Intestinal Peptide Tumors (VIPomas)

Sandostatin[®] (octreotide acetate) is indicated for the treatment of the profuse watery diarrhea associated with VIP-secreting tumors. Sandostatin[®] (octreotide acetate) studies were not designed to show an effect on the size, rate of growth or development of metastases.

CONTRAINDICATIONS

Sensitivity to this drug or any of its components.

WARNINGS

Single doses of Sandostatin[®] (octreotide acetate) have been shown to inhibit gallbladder contractility and decrease bile secretion in normal volunteers. In clinical trials (primarily patients with acromegaly or psoriasis), the incidence of biliary tract abnormalities was 63% (27% gallstones, 24% sludge without stones, 12% biliary duct dilatation). The incidence of stones or sludge in patients who received Sandostatin[®] (octreotide acetate) for 12 months or longer was 52%. Less than 2% of patients treated with Sandostatin[®] (octreotide acetate) for 1 month or less developed gallstones. The incidence of gallstones did not appear related to age, sex or dose. Like patients without gallbladder abnormalities, the majority of patients developing gallbladder abnormalities on ultrasound had gastrointestinal symptoms. The symptoms were not specific for gallbladder disease. A few patients developed acute cholecystitis, ascending cholangitis, biliary obstruction, cholestatic hepatitis, or pancreatitis during Sandostatin[®] (octreotide acetate) therapy or following its withdrawal. One patient developed ascending cholangitis during Sandostatin[®] (octreotide acetate) therapy and died.

PRECAUTIONS

General

Sandostatin[®] (octreotide acetate) alters the balance between the counter-regulatory hormones, insulin, glucagon and growth hormone, which may result in hypoglycemia or hyperglycemia. Sandostatin[®] (octreotide acetate) also suppresses secretion of thyroid stimulating hormone, which may result in hypothyroidism. Cardiac conduction abnormalities have also occurred during treatment with Sandostatin[®] (octreotide acetate). However, the incidence of these adverse events during long-term therapy was determined vigorously only in acromegaly patients who, due to their underlying disease and/or the subsequent treatment they receive, are at an increased risk for the development of diabetes mellitus, hypothyroidism, and cardiovascular disease. Although the degree to which these abnormalities are related to Sandostatin[®] (octreotide acetate) therapy is not clear, new abnormalities of glycemic control, thyroid function and ECG developed during Sandostatin[®] (octreotide acetate) therapy as described below.

The hypoglycemia or hyperglycemia which occurs during Sandostatin[®] (octreotide acetate) therapy is usually mild, but may result in overt diabetes mellitus or necessitate dose changes in insulin or other hypoglycemic agents. Hypoglycemia and hyperglycemia occurred

on Sandostatin[®] (octreotide acetate) in 3% and 16% of acromegalic patients, respectively. Severe hyperglycemia, subsequent pneumonia, and death following initiation of Sandostatin[®] (octreotide acetate) therapy was reported in one patient with no history of hyperglycemia.

In acromegalic patients, 12% developed biochemical hypothyroidism only, 8% developed goiter, and 4% required initiation of thyroid replacement therapy while receiving Sandostatin[®] (octreotide acetate). Baseline and periodic assessment of thyroid function (TSH, total and/or free T₄) is recommended during chronic therapy.

In acromegalics, bradycardia (<50 bpm) developed in 25%; conduction abnormalities occurred in 10% and arrhythmias occurred in 9% of patients during Sandostatin[®] (octreotide acetate) therapy. Other EKG changes observed included QT prolongation, axis shifts, early repolarization, low voltage, R/S transition, and early R wave progression. These ECG changes are not uncommon in acromegalic patients. Dose adjustments in drugs such as beta-blockers that have bradycardia effects may be necessary. In one acromegalic patient with severe congestive heart failure, initiation of Sandostatin[®] (octreotide acetate) therapy resulted in worsening of CHF with improvement when drug was discontinued. Confirmation of a drug effect was obtained with a positive rechallenge.

Several cases of pancreatitis have been reported in patients receiving Sandostatin[®] (octreotide acetate) therapy.

Sandostatin[®] (octreotide acetate) may alter absorption of dietary fats in some patients.

In patients with severe renal failure requiring dialysis, the half-life of Sandostatin[®] (octreotide acetate) may be increased, necessitating adjustment of the maintenance dosage.

Depressed vitamin B₁₂ levels and abnormal Schilling's tests have been observed in some patients receiving Sandostatin[®] (octreotide acetate) therapy, and monitoring of vitamin B₁₂ levels is recommended during chronic Sandostatin[®] (octreotide acetate) therapy.

Information for Patients

Careful instruction in sterile subcutaneous injection technique should be given to the patients and to other persons who may administer Sandostatin[®] (octreotide acetate) Injection.

Laboratory Tests

Laboratory tests that may be helpful as biochemical markers in determining and following patient response depend on the specific tumor. Based on diagnosis, measurement of the following substances may be useful in monitoring the progress of therapy:

Acromegaly: Growth Hormone, IGF-I (somatomedin C) Responsiveness to Sandostatin[®] (octreotide acetate) may be evaluated by determining growth hormone levels at 1-4 hour intervals for 8-12 hours post dose. Alternatively, a single measurement of IGF-I (somatomedin C) level may be made two weeks after drug initiation or dosage change.

Carcinoid: 5-HIAA (urinary 5-hydroxyindole acetic acid), plasma serotonin, plasma Substance P

VIPoma: VIP (plasma vasoactive intestinal peptide)

Baseline and periodic total and/or free T₄ measurements should be performed during chronic therapy (*see PRECAUTIONS – General*).

Drug Interactions

Sandostatin[®] (octreotide acetate) has been associated with alterations in nutrient absorption, so it may have an effect on absorption of orally administered drugs. Concomitant administration of Sandostatin[®] (octreotide acetate) with cyclosporine may decrease blood levels of cyclosporine and result in transplant rejection.

Patients receiving insulin, oral hypoglycemic agents, beta blockers, calcium channel blockers, or agents to control fluid and electrolyte balance, may require dose adjustments of these therapeutic agents.

Drug Laboratory Test Interactions

No known interference exists with clinical laboratory tests, including amine or peptide determinations.

Carcinogenesis/Mutagenesis/Impairment of Fertility

Studies in laboratory animals have demonstrated no mutagenic potential of Sandostatin[®] (octreotide acetate).

No carcinogenic potential was demonstrated in mice treated subcutaneously for 85-99 weeks at doses up to 2000 mcg/kg/day (8x the human exposure based on body surface area). In a 116-week subcutaneous study in rats, a 27% and 12% incidence of injection site sarcomas or squamous cell carcinomas was observed in males and females, respectively, at the highest dose level of 1250 mcg/kg/day (10x the human exposure based on body surface area) compared to an incidence of 8%-10% in the vehicle-control groups. The increased incidence of injection site tumors was most probably caused by irritation and the high sensitivity of the rat to repeated subcutaneous injections at the same site. Rotating injection sites would prevent chronic irritation in humans. There have been no reports of injection site tumors in patients treated with Sandostatin[®] (octreotide acetate) for up to 5 years. There was also a 15% incidence of uterine adenocarcinomas in the 1250 mcg/kg/day females compared to 7% in the saline-control females and 0% in the vehicle-control females. The presence of endometritis coupled with the absence of corpora lutea, the reduction in mammary fibroadenomas, and the presence of uterine dilatation suggest that the uterine tumors were associated with estrogen dominance in the aged female rats which does not occur in humans.

Sandostatin[®] (octreotide acetate) did not impair fertility in rats at doses up to 1000 mcg/kg/day, which represents 7x the human exposure based on body surface area.

Pregnancy Category B

Reproduction studies have been performed in rats and rabbits at doses up to 16 times the highest human dose based on body surface area and have revealed no evidence of impaired fertility or harm to the fetus due to Sandostatin[®] (octreotide acetate). There are, however, no

adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in milk, caution should be exercised when Sandostatin[®] (octreotide acetate) is administered to a nursing woman.

Pediatric Use

Experience with Sandostatin[®] (octreotide acetate) in the pediatric population is limited. Although formal controlled clinical trials have not been performed to evaluate safety and effectiveness in this age group, there are reports of 49 cases in the literature of neonates and infants with congenital hyperinsulinism [also called familial hyperinsulinism (HI), persistent hyperinsulinemic hypoglycemia of infancy (PHHI), or nesidioblastosis] who have received Sandostatin[®] as an inhibitor of insulin release. The following efficacy and safety information is derived from these 49 patients.

Sandostatin[®] has been used to stabilize plasma glucose levels prior to pancreatectomy and to treat recurrent post-operative hypoglycemia. Although most use of octreotide in this setting is short-term, a few reports in the literature have documented longer-term therapy in pediatric patients (2.2-5.5 years). Octreotide is an alternative medical treatment to diazoxide for control of hypoglycemia in this disorder. Of 31 pediatric patients who received Sandostatin[®] as prescribed for congenital hyperinsulinism and for which long-term follow-up was available, octreotide obviated the need for surgery in 3 patients (10%) and was replaced by diazoxide in 4 patients (13%) due to uncontrolled hypoglycemia. Although the remainder of these patients required surgery, there have been a few reports in the literature of patients who have responded to octreotide after failing treatment with surgery and/or diazoxide. Doses of 3-40 mcg/kg/day have been used. At these doses, the majority of side effects were gastrointestinal: diarrhea, steatorrhea, vomiting, and abdominal distention, each reported in 22%-35% (n = 11-17) of patients. However, they were generally short-lived – with resolution of vomiting and distention in 2-4 days, and diarrhea/steatorrhea, within 2-4 weeks. Steatorrhea was controlled in most patients with pancreatic enzyme supplements. Poor growth was reported in 37% of patients (n = 7) who received Sandostatin[®] for 1-4.33 years. It was associated with low serum growth hormone and/or IGF-1 levels in 4/6 patients in whom these parameters were measured. Catch-up growth occurred in 3/3 patients who were followed after Sandostatin[®] was discontinued. Poor weight gain was reported in 32% of patients (n = 6). Tachyphylaxis was reported in 35% (n = 17) of patients. Asymptomatic gallstones with sludge was reported in one infant after one year of therapy and was treated with ursodeoxycholic acid. There has been a single report of an infant with nesidioblastosis who experienced a seizure thought to be independent of Sandostatin[®] therapy. A single death has been reported in a 16-month-old male with enterocutaneous fistula who developed sudden abdominal pain and increased nasogastric drainage and expired 8 hours after receiving a single 100 mcg subcutaneous dose of Sandostatin[®].

ADVERSE REACTIONS

Gallbladder Abnormalities

Gallbladder abnormalities, especially stones and/or biliary sludge, frequently develop in patients on chronic Sandostatin[®] (octreotide acetate) therapy (*see WARNINGS*).

Cardiac

In acromegalics, sinus bradycardia (<50 bpm) developed in 25%; conduction abnormalities occurred in 10% and arrhythmias developed in 9% of patients during Sandostatin[®] (octreotide acetate) therapy (*see PRECAUTIONS – General*).

Gastrointestinal

Diarrhea, loose stools, nausea and abdominal discomfort were each seen in 34%-61% of acromegalic patients in U.S. studies although only 2.6% of the patients discontinued therapy due to these symptoms. These symptoms were seen in 5%-10% of patients with other disorders.

The frequency of these symptoms was not dose-related, but diarrhea and abdominal discomfort generally resolved more quickly in patients treated with 300 mcg/day than in those treated with 750 mcg/day. Vomiting, flatulence, abnormal stools, abdominal distention, and constipation were each seen in less than 10% of patients.

Hypo/Hyperglycemia

Hypoglycemia and hyperglycemia occurred in 3% and 16% of acromegalic patients, respectively, but only in about 1.5% of other patients. Symptoms of hypoglycemia were noted in approximately 2% of patients.

Hypothyroidism

In acromegalics, biochemical hypothyroidism alone occurred in 12% while goiter occurred in 6% during Sandostatin[®] (octreotide acetate) therapy (*see PRECAUTIONS – General*). In patients without acromegaly, hypothyroidism has only been reported in several isolated patients and goiter has not been reported.

Other Adverse Events

Pain on injection was reported in 7.7%, headache in 6% and dizziness in 5%. Pancreatitis was also observed (*see WARNINGS and PRECAUTIONS*).

Other Adverse Events 1%-4%

Other events (relationship to drug not established), each observed in 1%-4% of patients, included fatigue, weakness, pruritus, joint pain, backache, urinary tract infection, cold symptoms, flu symptoms, injection site hematoma, bruise, edema, flushing, blurred vision, pollakiuria, fat malabsorption, hair loss, visual disturbance and depression.

Other Adverse Events <1%

Events reported in less than 1% of patients and for which relationship to drug is not established are listed: *Gastrointestinal*: hepatitis, jaundice, increase in liver enzymes, GI bleeding, hemorrhoids, appendicitis, gastric/peptic ulcer, gallbladder polyp; *Integumentary*: rash, cellulitis, petechiae, urticaria, basal cell carcinoma; *Musculoskeletal*: arthritis, joint effusion, muscle pain, Raynaud's phenomenon; *Cardiovascular*: chest pain, shortness of breath, thrombophlebitis, ischemia, congestive heart failure, hypertension, hypertensive reaction, palpitations, orthostatic BP decrease, tachycardia; *CNS*: anxiety, libido decrease, syncope, tremor, seizure, vertigo, Bell's Palsy, paranoia, pituitary apoplexy, increased intraocular pressure, amnesia, hearing loss, neuritis; *Respiratory*: pneumonia, pulmonary nodule, status asthmaticus; *Endocrine*: galactorrhea, hypoadrenalism, diabetes insipidus, gynecomastia, amenorrhea, polymenorrhea, oligomenorrhea, vaginitis; *Urogenital*: nephrolithiasis, hematuria; *Hematologic*: anemia, iron deficiency, epistaxis; *Miscellaneous*: otitis, allergic reaction, increased CK, weight loss.

Evaluation of 20 patients treated for at least 6 months has failed to demonstrate titers of antibodies exceeding background levels. However, antibody titers to Sandostatin[®] (octreotide acetate) were subsequently reported in three patients and resulted in prolonged duration of drug action in two patients. Anaphylactoid reactions, including anaphylactic shock, have been reported in several patients receiving Sandostatin[®] (octreotide acetate).

OVERDOSAGE

No frank overdose has occurred in any patient to date. Intravenous bolus doses of 1 mg (1000 mcg) given to healthy volunteers and of 30 mg (30,000 mcg) IV over 20 minutes and of 120 mg (120,000 mcg) IV over 8 hours to research patients have not resulted in serious ill effects.

Up-to-date information about the treatment of overdose can often be obtained from a certified Regional Poison Control Center. Telephone numbers of certified Regional Poison Control Centers are listed in the Physicians' Desk Reference[®].*

Mortality occurred in mice and rats given 72 mg/kg and 18 mg/kg IV, respectively.

Drug Abuse and Dependence

There is no indication that Sandostatin[®] (octreotide acetate) has potential for drug abuse or dependence. Sandostatin[®] (octreotide acetate) levels in the central nervous system are negligible, even after doses up to 30,000 mcg.

DOSAGE AND ADMINISTRATION

Sandostatin[®] (octreotide acetate) may be administered subcutaneously or intravenously. Subcutaneous injection is the usual route of administration of Sandostatin[®] (octreotide acetate) for control of symptoms. Pain with subcutaneous administration may be reduced by using the smallest volume that will deliver the desired dose. Multiple subcutaneous injections

at the same site within short periods of time should be avoided. Sites should be rotated in a systematic manner.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. **Do not use if particulates and/or discoloration are observed.** Proper sterile technique should be used in the preparation of parenteral admixtures to minimize the possibility of microbial contamination. **Sandostatin® (octreotide acetate) is not compatible in Total Parenteral Nutrition (TPN) solutions because of the formation of a glycosyl octreotide conjugate which may decrease the efficacy of the product.**

Sandostatin® (octreotide acetate) is stable in sterile isotonic saline solutions or sterile solutions of dextrose 5% in water for 24 hours. It may be diluted in volumes of 50-200 mL and infused intravenously over 15-30 minutes or administered by IV push over 3 minutes. In emergency situations (e.g.: carcinoid crisis) it may be given by rapid bolus.

The initial dosage is usually 50 mcg administered twice or three times daily. Upward dose titration is frequently required. Dosage information for patients with specific tumors follows.

Acromegaly

Dosage may be initiated at 50 mcg t.i.d. Beginning with this low dose may permit adaptation to adverse gastrointestinal effects for patients who will require higher doses. IGF-I (somatomedin C) levels every 2 weeks can be used to guide titration. Alternatively, multiple growth hormone levels at 0-8 hours after Sandostatin® (octreotide acetate) administration permit more rapid titration of dose. The goal is to achieve growth hormone levels less than 5 ng/mL or IGF-I (somatomedin C) levels less than 1.9 U/mL in males and less than 2.2 U/mL in females. The dose most commonly found to be effective is 100 mcg t.i.d., but some patients require up to 500 mcg t.i.d. for maximum effectiveness. Doses greater than 300 mcg/day seldom result in additional biochemical benefit, and if an increase in dose fails to provide additional benefit, the dose should be reduced. IGF-I (somatomedin C) or growth hormone levels should be re-evaluated at 6-month intervals.

Sandostatin® (octreotide acetate) should be withdrawn yearly for approximately 4 weeks from patients who have received irradiation to assess disease activity. If growth hormone or IGF-I (somatomedin C) levels increase and signs and symptoms recur, Sandostatin® (octreotide acetate) therapy may be resumed.

Carcinoid Tumors

The suggested daily dosage of Sandostatin® (octreotide acetate) during the first 2 weeks of therapy ranges from 100-600 mcg/day in 2-4 divided doses (mean daily dosage is 300 mcg). In the clinical studies, the **median** daily maintenance dosage was approximately 450 mcg, but clinical and biochemical benefits were obtained in some patients with as little as 50 mcg, while others required doses up to 1500 mcg/day. However, experience with doses above 750 mcg/day is limited.

VIPomas

Daily dosages of 200-300 mcg in 2-4 divided doses are recommended during the initial 2 weeks of therapy (range 150-750 mcg) to control symptoms of the disease. On an individual basis, dosage may be adjusted to achieve a therapeutic response, but usually doses above 450 mcg/day are not required.

HOW SUPPLIED

Sandostatin® (octreotide acetate) Injection is available in 1 mL ampuls and 5 mL multi-dose vials as follows:

Ampuls

50 mcg/mL octreotide (as acetate)

Package of 10 ampuls NDC 0078-0180-01

100 mcg/mL octreotide (as acetate)

Package of 10 ampuls NDC 0078-0181-01

500 mcg/mL octreotide (as acetate)

Package of 10 ampuls NDC 0078-0182-01

Multi-Dose Vials

200 mcg/mL octreotide (as acetate)

Box of one NDC 0078-0183-25

1000 mcg/mL octreotide (as acetate)

Box of one NDC 0078-0184-25

Storage

For prolonged storage, Sandostatin® (octreotide acetate) ampuls and multi-dose vials should be stored at refrigerated temperatures 2°C-8°C (36°F-46°F) and protected from light. At room temperature, (20°C-30°C or 70°F-86°F), Sandostatin® (octreotide acetate) is stable for 14 days if protected from light. The solution can be allowed to come to room temperature prior to administration. Do not warm artificially. After initial use, multiple-dose vials should be discarded within 14 days. Ampuls should be opened just prior to administration and the unused portion discarded.

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T2002-82

REV: OCTOBER 2002

89017902

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Manufactured by:
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Schaffhauserstrasse
CH-4332 Stein, Switzerland

Distributed by:
Novartis Pharmaceuticals Corporation
East Hanover, NJ 07936

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